Docket No. 2551-1-001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Hassan Ahmad & Ismail Elchagea

EXAMINER: McCormick Ewoldt, Susan Beth

SERIAL NO.: 10/662,777

ART UNIT: 1654

FILED: September 15, 2003

TITLE: BOTANICAL DRUG COMPOSITIONS FOR TREATMENT OF LIVER AND IMMUNOLOGICAL DISORDERS

CERTIFICATE OF MAILING UNDER 37 CFR 1.8

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on June 29, 2005.

Loretta Kavanagh
(Name of person Depositing Mail)

Loretta Kavanagh 6/29/05
(Signature and Date)

DECLARATION PURSUANT TO 37 C.F.R. § 1.132 OF ISMAIL ELCHAGEA, PH.D.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Ismail Elchagea, do hereby declare as follows:

1. I am President and Chief Operating Officer and Co-founder of Ambotan Pharma that specializes in developing drugs in the area of life threatening disease categories, especially HCV. I am also the Founder, Chairman of the Board and CEO of ITPL Laboratories that provides analytical and formulation services to the Pharmaceutical Industry.

2. My principal area of research is in Natural Products and Pharmaceutical Research and Drug Development, with particular expertise in infectious diseases.

3. In the course of my activities, I have been listed as an inventor on the present patent application, entitled "BOTANICAL DRUG COMPOSITIONS FOR TREATMENT OF LIVER AND IMMUNOLOGICAL DISORDERS", having U.S. Serial Number 10/662,777, filed September 15, 2003.

4. I have reviewed the disclosure of the present application, with particular emphasis on the pharmaceutical compositions under development for treating patients with advanced stage liver disease and immunological disorders. Our laboratory has identified the plants and extracts of this application as being efficacious for treating patients having advanced stage hepatitis, which is characterized as being of stage 4-6, with evidence of fibrosis and cirrhosis of the liver.

5. To my knowledge there are no effective therapies to reverse or stabilize the liver damage observed in this late stage of hepatitis. Furthermore, to my knowledge, no others have used the plants or plant extracts of the present invention to stabilize or reverse the histopathological effects of hepatitis, including liver fibrosis and cirrhosis associated with stages 4-6 of hepatitis.

6. Upon review of the references by Shawkat and by Medenica, I do not find evidence that they have studied hepatitis patients in this very late stage of the disease process. More particularly, they do not demonstrate the use of any of the plants for treating hepatitis patients in stages 4-6 having signs of fibrosis or cirrhosis, or for reversing the histopathological changes in the liver of these patients.

7. Furthermore, neither Shawkat nor Medenica demonstrate the use of the plants of the present invention, including *Nigella sativa*, for elevating either the number or activity of immune cells or platelets in advanced stage (stages 4-6) hepatitis patients having fibrosis or cirrhosis.

8. Our laboratory has demonstrated the ability to stabilize or to reverse the progression of pathological changes in the liver and to increase the immune cell number and activity of these cells in patients having stage 4-6 of type C hepatitis, genotype 4, when the plant extracts of the present invention are used at a concentration of not less than 20% w/v. These findings are unexpected, given the serious nature of the disease at such a late stage. We were only able to observe the unexpected results in improvement of liver function tests, improved histopatholgy and improvement in immune cell number and function in this patient population by increasing the dosages to at least 20% w/v. Lower doses such as those used by Shawkat and Medenica were not effective in reversing the histopathology or immune function or immune cell numbers in these patients. Shawkat and Medenica would not know to use the increased dosage of the extracts, such as those used in our studies, since the patient population studied by Shawkat and Medenica in all likelihood were not patients in the advanced stage of hepatitis and did not have the fibrosis or cirrhosis as exhibited by the patients in our studies.

9. The results of the clinical trials using these plant extracts for treating stage 4-6 hepatitis patients with fibrosis and cirrhosis are attached here as Exhibit A. In our clinical studies, patients having greater than 2 million copies of HepC genotype 4 were randomized to Placebo (P) or Ambovex (Amb) treatment groups. A number of studies were conducted, lasting from 6 months through 24 months. Ambovex patients, but not placebo patients, showed lowering of the viral load, as shown by the decrease of hepatitis virus RNA (Figure 1). Furthermore, Ambovex patients, but not placebo patients, showed improvements in liver function tests, including ALT and AST (Figure 2). In addition, Figures 3 through 6 demonstrate the dramatic impact of Ambovex on fibrotic progression in the liver. Moreover, Figure 5 shows the more specific and significant effects of Ambovex on staging, hepatic activity index (HAI), and the presence of reticulin and collagenosis in this patient population. Figure 6 provides a summary of the number of patients that improved, stabilized or worsened during the course of the clinical study. Figures 7-10 show that the administration of Ambovex to advanced stage hepatitis

patients has a significant impact on the number of immune cells and their activity, including natural killer cells (NK), macrophages, and T cells, as well as an increase in the number of platelets. It is evident that the findings of our studies are very dramatic given the advanced stage of the disease being treated. Neither Shawkat nor Medenica demonstrate an effect of the plants of our present invention on any of these parameters in patients having advanced stage hepatitis with liver fibrosis or cirrhosis. Nor could they have observed such dramatic effects at the lower doses they used, since our findings indicate that doses of at least 20% w/v are necessary to stabilize or reverse the histopathology and immune functions in this patient population.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Title 18 of the U.S. Code, Section 1001, and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Dated: 6/27/05

Ismail Elchagea, Ambotan Pharma,
President and Chief Operating Officer

FIGURE 1

Ambovex impact on PCR/RNA of first group cases compared with placebo

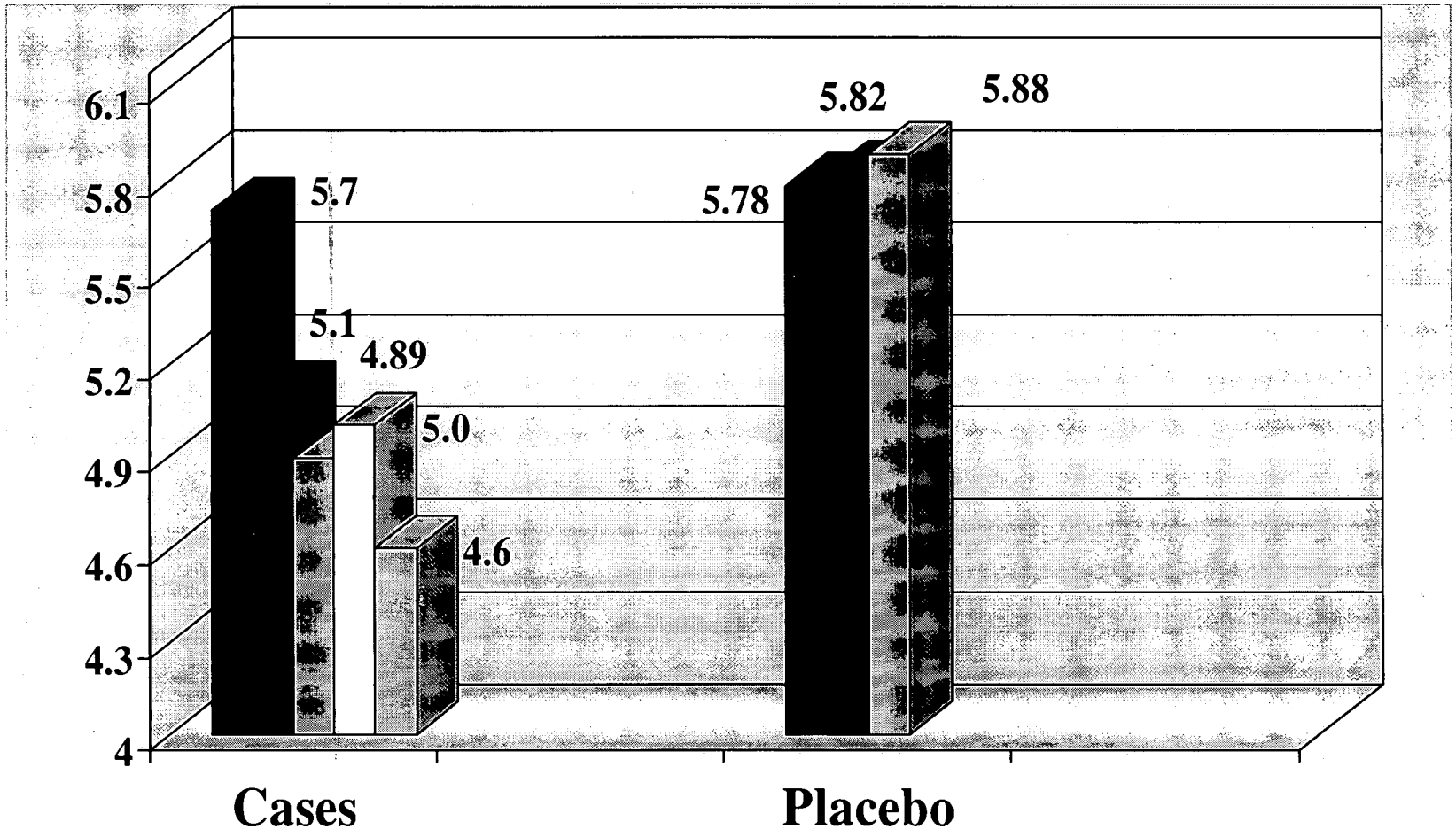


FIGURE 2

Liver Function Tests

Groups	ALT	AST
First Group N= 59		
p Value (6 Months)	< 0.0001	< 0.0001
p Value (12 Months)	< 0.0001	< 0.0001
p Value (24 Months)	< 0.0001	< 0.0001
Placebo		
p Value (6 Months)	0.8	0.8
p Value (12 Months)	-	-

FIGURE 3

Ambovex impact on fibrotic progression of first group cases compared with placebo

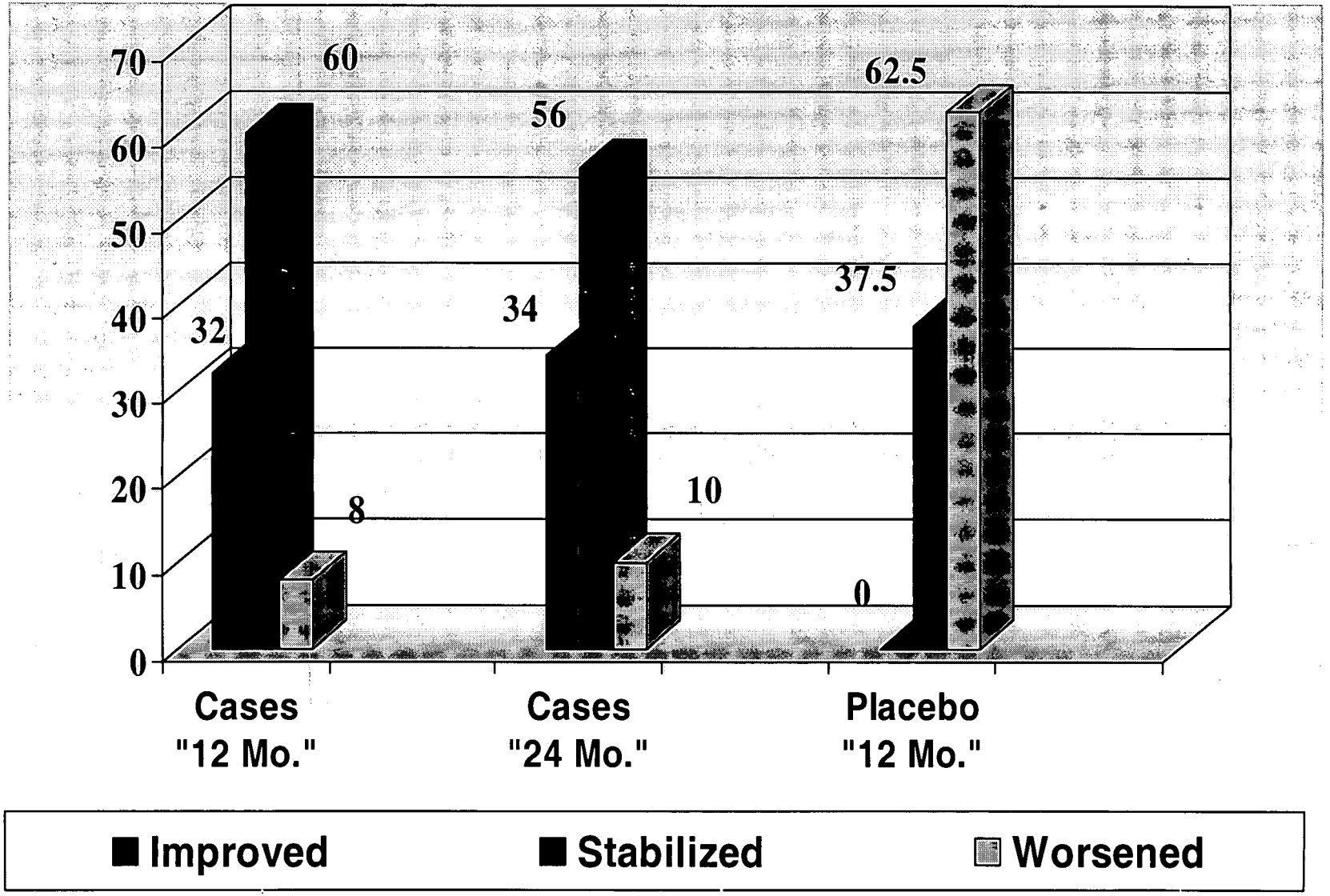


FIGURE 4

Ambovex impact on fibrotic stages of first group cases compared with placebo

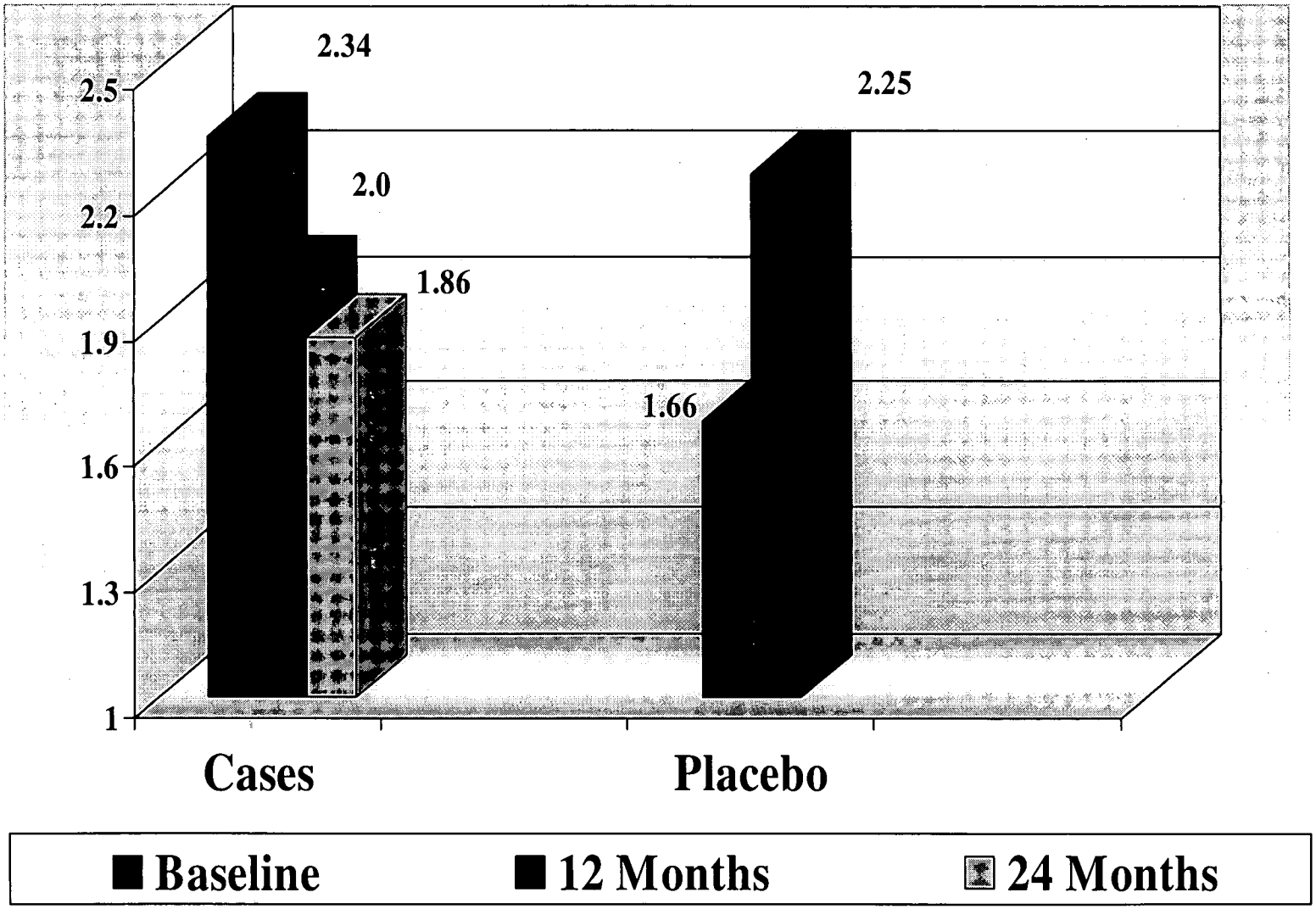


FIGURE 5

HISTOPATHOLGY

Categories	First group (24 Months) N=59			Third group N=15	
	Baseline	12 Months	24 Months	Baseline	6 Months
STAGE					
Mean ± SD	2.34 ± 0.21	2.0 ± 0.2	1.86 ± 0.2	1.5 ± 0.3	1.2 ± 0.2
p Value	-	< 0.0001	< 0.0001	-	0.0005
HAI					
Mean ± SD	5.98 ± 0.36	5.88 ± 0.39	4.55 ± 0.5	5.5 ± 0.76	5.0 ± 0.8
p Value	-	< 0.0001	< 0.0001	-	0.008
RETICULIN					
Mean ± SD	1.8 ± 0.16	1.5 ± 0.14	1.2 ± 0.18	0.6 ± 0.24	0.9 ± 0.2
p Value	-	< 0.0001	< 0.0001	-	0.4
COLLAGENOSIS					
Mean ± SD	2.04 ± 0.13	1.6 ± 0.14	1.7 ± 0.17	1.08 ± 0.18	1.29 ± 0.18
p Value	-	< 0.0001	< 0.0001	-	0.4

FIGURE 6

Changes in Pathological Stages

Changes in Pathological Stages	First group (24 Months) N=59				Third Group (6 Months) N= 15	
	12 Months		24 Months		6 Months	
	No.	%	No.	%	No.	%
Improved	14	32	13	34	5	42
Stabilized	27	60	22	56	6	50
Worsened	4	8	4	10	1	8
Total number	45		39		12	

FIGURE 7

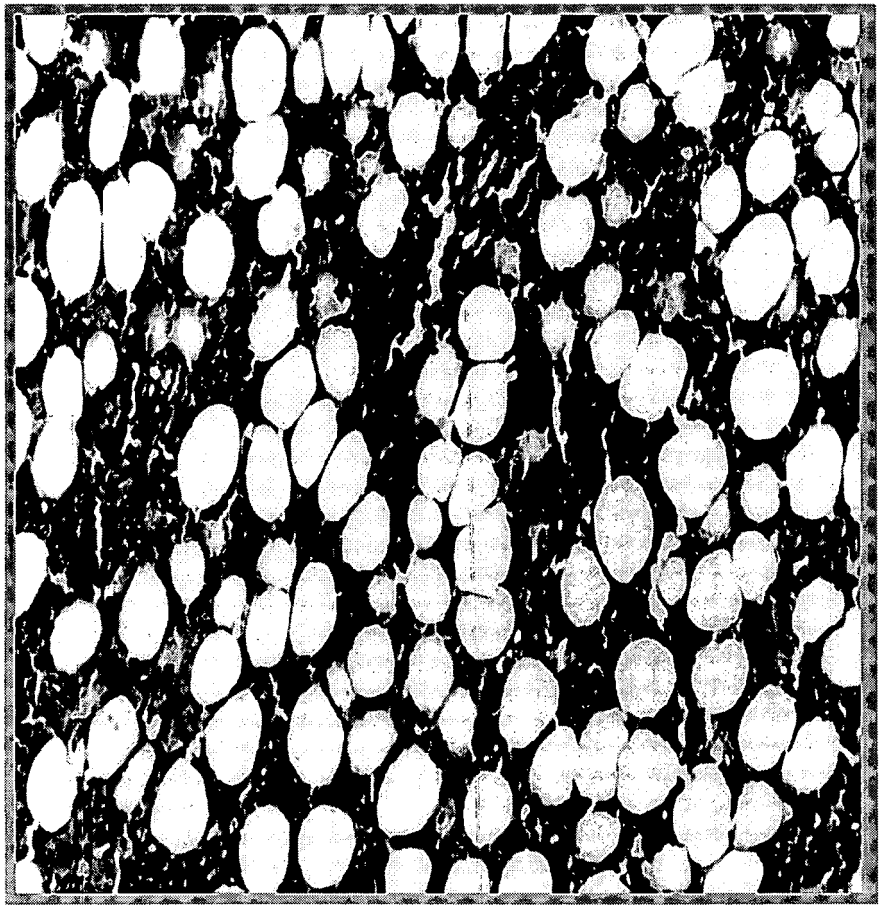
IMMUNOPATHOLOGY

Categories	First group (24 Months) N=59			Third Group (6 Months) N=15	
	Baseline	12 Months	24 Months	Baseline	6 Months
BAN T (CD 43)	29.5 ± 5.1	40.45 ± 9.6	68 ± 5.8	60.1 ± 9.27	58.2 ± 9.27
p Value	-	0.7	0.01	-	0.8
Macrophage & Von Kupffer Cells	2.6 ± 0.4	9.18 ± 2.3	17.4 ± 1.3	13.7 ± 2.3	15.66 ± 2.3
p Value	-	0.01	< 0.0001	-	0.56
Activation of Macrophage & Von Kupffer Cells	0.0 ± 0.0	2.1 ± 0.29	2.25 ± 0.36	1.66 ± 0.3	1.62 ± 0.3
p Value	-	0.01	< 0.0001	-	0.9
Natural Killer Cells (CD 57)	9.9 ± 0.91	32 ± 5.8	4.37 ± 1.2	6.16 ± 1.8	6.75 ± 1.8
p Value	-	0.001	0.001	-	0.8

FIGURE 8

Histological effects on rat's Bone Marrow

Bone Marrow Without Treatment



Bone Marrow With Treatment

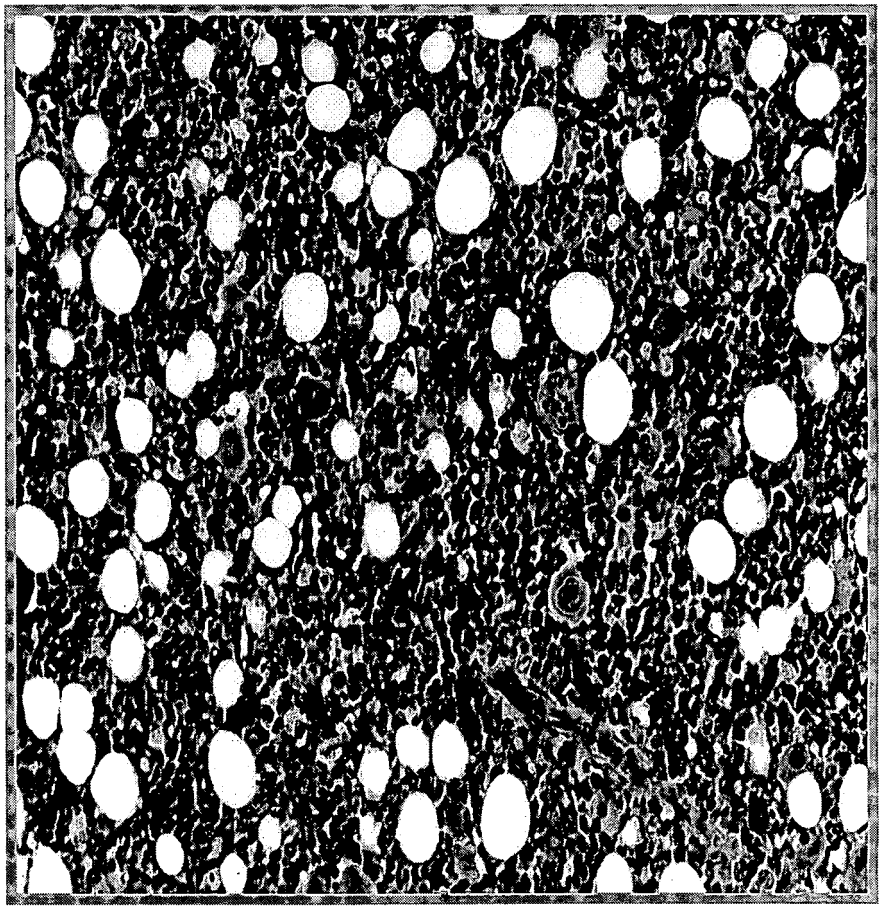
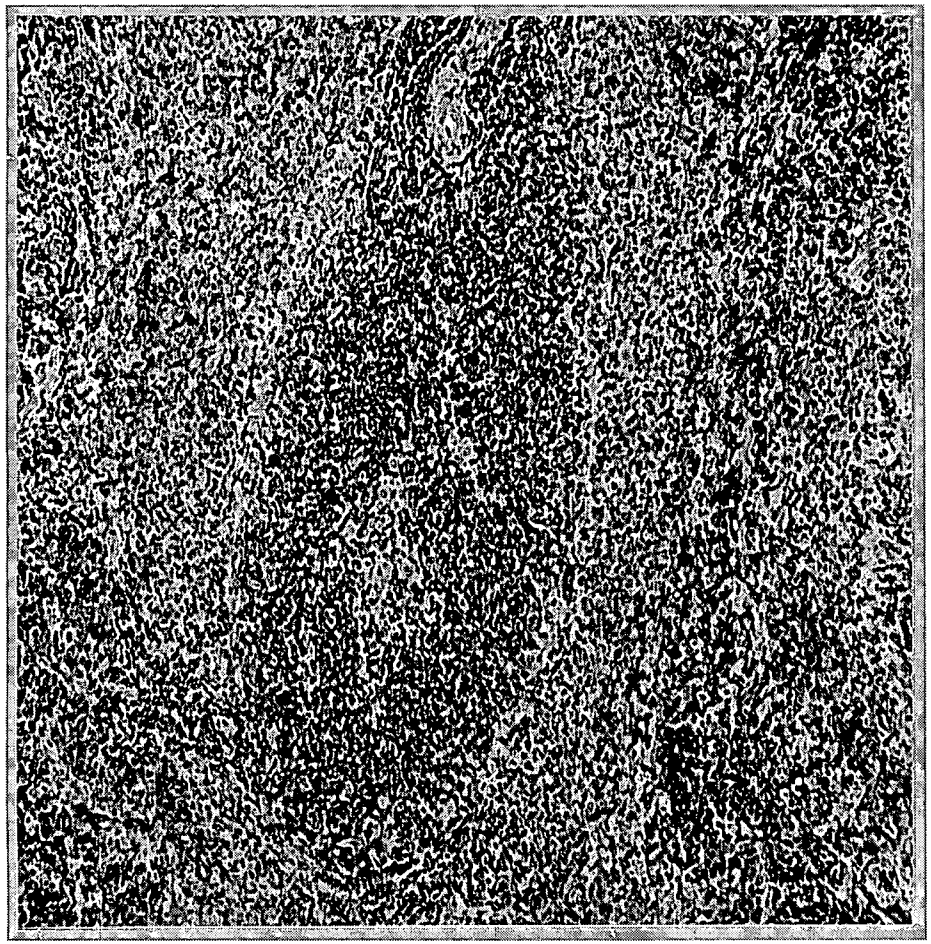


FIGURE 9

Histological effects on rat's Spleen

Spleen Without Treatment



Spleen With Treatment

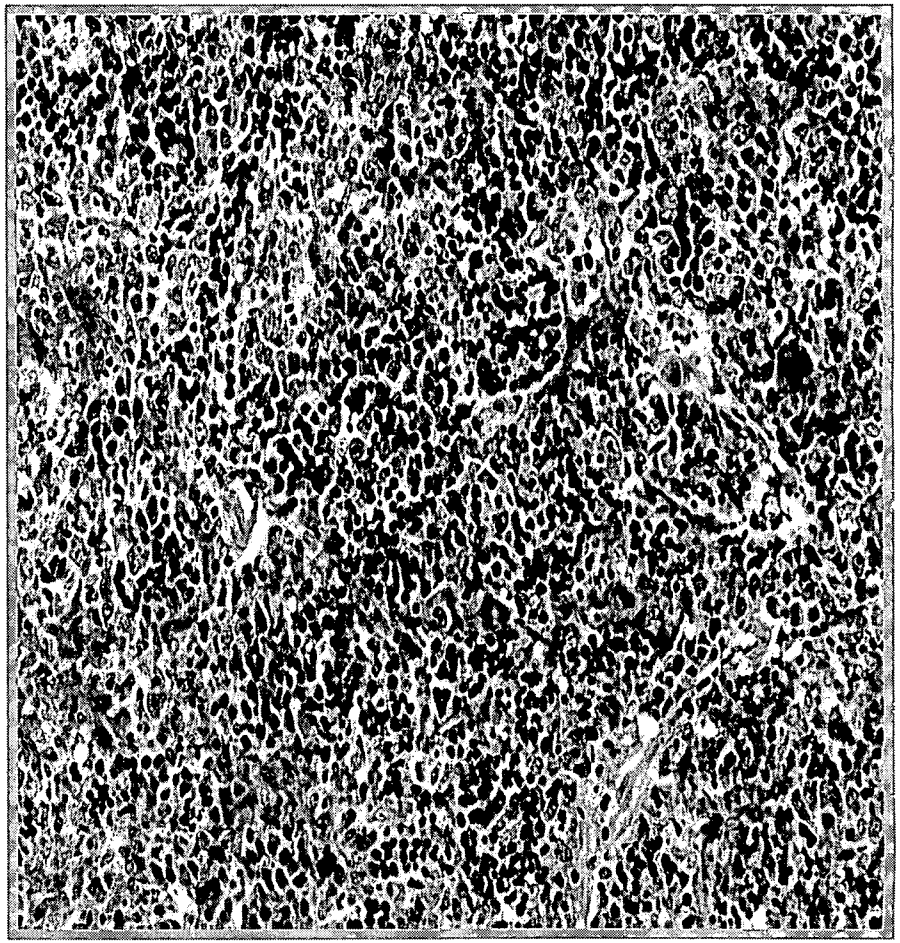


FIGURE 10

Coagulant and Red & White Blood Count Responses

Categories	First group (24 Months) N=59	Second Group (12 Months) N=42	Third group (6 Months) N=15
	p Value		
Prothrombin	0.44	1.0	0.25
Hemoglobin	0.06	0.1	0.16
Red Blood Cells	0.73	-	0.2
Hematocrit	0.01	-	0.12
MCV	0.09	-	0.16
MCH	0.12	-	0.2
MCHC	0.05	-	1.0
Platelets	0.05	0.004	0.01
Total Lecksytic Count	0.06	0.0	0.25
Neutrophils Segmented	0.009	-	0.0
Neutrophils Juvenile	0.7	-	0.45
Lymphocytes	0.02	-	0.17
Monocytes	0.9	-	1.0
Eosinophils	0.29	-	0.0
Basophiles	1.0	-	0.0